### Original Investigation

# Novel markers of doppler ultrasonography in the placenta accreta spectrum to predict complications

Fahimeh Gotbizadeh Vahdani<sup>1</sup>, Azadeh Shabani<sup>2</sup>, Mohammad Haddadi<sup>3</sup>,

Seyedeh Mojgan Ghalandarpoor-Attar<sup>4</sup>,
Zahra Panahi<sup>1</sup>,
Sedigheh Hantoushzadeh<sup>3</sup>,
Sedighe Borna<sup>3</sup>,
Maryam Deldar Pasikhani<sup>1</sup>,
Sanaz Ghashghaee<sup>5</sup>,
Mamak Shariat<sup>6</sup>

<sup>1</sup>Maternal-fetal and Neonatal Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran <sup>2</sup>Preventiative Gynecology Research Center (PGRC), OBGYN Department, Shahid Beheshti University of Medical Science, Arabi Ave, İran <sup>3</sup>Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran <sup>4</sup>Obstetrics and gynecology department, Baharloo hospital, Tehran University of Medical Sciences

<sup>5</sup>Department of Obstetrics and Gynecology, Vali-E-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran <sup>6</sup>Breastfeeding Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran

### Abstract

**Objective:** Ultrasonography is an acceptable tool to diagnose the placenta accreta spectrum (PAS) among pregnant women; however, the lack of a strong criteria protocol in diagnosis and predicting the severity of the consequences facing pregnant women requires novel markers investigation.

**Material and Methods:** This prospective cross-sectional study was performed on pregnant women with a probable diagnosis of PAS. Therefore, 51 pregnant women were involved in the study. Their characteristic information, medical and surgical history, blood loss severity(severe:>=2500 ml), following hysterectomy, and the histopathology after the surgery were collected. Also, the Doppler of right and left uterine arteries, including the pulsatility index(PI), resistance Index(RI), peak systolic velocity(PSV), the PSV of the posterior part of the bladder, cervix, the largest lacuna, and the posterior lacuna of the bladder were calculated by Doppler ultrasonography. Data were analyzed to investigate the relationship between Doppler markers and the severity of PAS(bleeding, hysterectomy, pathology).

**Results:** The mean age of the pregnant women was  $35.4 \pm 4.11$  (median:35.00) years. 17(33.3%) of pregnant women had severe Bleeding. The median of bladder PSV, cervix PSV, and left uterine artery for women with severe bleeding were 57.00(34,90), 26.00(0,63), and 89.00(81,135), while there were 33.00(20,64), 18.00(0.76), and 68.00(61,113) for women without severe bleeding (p-value: < 0.001, 0.037, 0.045). 34 (66.66%) pregnant women had hysterectomy. Bladder PSV, cervix PSV, and left uterine PSV for women with hysterectomy were 46.00(20,90), 20.00(0,76), and 68.00(61,135) compared to 39.50(33,46), 20.00(14,26), and 82.00(63,101) for women without (p-value=0.005, 0.013, 0.003).

**Conclusion:** Bladder PSV, cervix PSV, and uterine PSV are significantly higher in pregnant women with PSV, and they can be appropriate markers in diagnosing PAS and predicting its severity. So that healthcare providers could use them to make better clinical decisions.

Keywords: Doppler ultrasonography, hysterectomy, hemorrhage, PAS, placenta accreta spectrum, PSV

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### Introduction

The placenta accreta spectrum (PAS) is a spectrum situation distinguished by unexpected adherence of the placenta to its

implantation site. It includes accreta, increta, and percreta. Its pathology is unknown; however, placenta previa and earlier uterine surgery can be significant risk factors for the condition (1,2). Cesarean delivery as a uterine surgery is increasing in

e.mail: azadeshabani@sbmu.ac.ir ORCID: orcid.org/0000-0003-3779-9218

Address for Correspondence: Azadeh Shabani

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many countries; therefore, the rate of PAS is increasing by a higher cesarean delivery rate (3). The incidence of PAS is 0.91%(4); also,1 in 313 women with previous cesarean delivery had been diagnosed with PAS (5). Obstetric bleeding and surgical issues such as hysterectomy are the significant complications facing women with PAS; in addition, posttraumatic d isorders(PTSD), other psychological complications, and more prolonged hospital admission are noticed among pregnant women with PAS (6).

Histopathology is the gold standard in diagnosing PAS (2); however, ultrasonography (US) is common in diagnosing and evaluating the severity of the complications facing pregnant women; it is insufficient, especially in pregnant women with the posterior placenta (7). Moreover, Magnetic resonance imaging (MRI) can be an appropriate choice for pregnant women with PAS that is difficult to evaluate by ultrasonography (8).

The Society for Maternal-Fetal Medicine (SMFM) in 2021 suggested different sonographic markers for PAS for each trimester, such as cesarian scar and low implantation pregnancy in first trimesters, placenta lacuna, Abnormal uteroplacental interface, Abnormal uterine contour (placental bulge), and Exophytic mass(9).

Doppler US is a sonography method based on differences in ultrasound frequency when an object moves without consequences on the maternal-fetal issue (10). Collins et al. reported that markers in 3D color Doppler sonography had effective means to diagnose PAS, and it could predict the severity (11). Moreover, Hossein et al. showed that specific markers in 2D and 3D Doppler could predict the severity and consequences of hysterectomy and bleeding in pregnant women with PAS disorders (12). Also, SMFM considered Bridging vessels (blood vessels lengthened from the placenta across the myometrium) as a Doppler US marker for PAS. Still, it indicated that the role of Doppler US is a research gap in diagnosing PAS and requires more study to clarify (9).

In our study, we aim to investigate the role of Doppler US in pregnant women with PAS. We intend to evaluate the significance of novel markers in this diagnostic method by complications facing pregnant women; therefore, clinicians can choose the appropriate procedures to decrease morbidities and mortality among pregnant women.

### **Materials and Methods**

After ethical committee approval, this prospective crosssectional study was performed in the third referral center from September 2021 to August 2022. The population was pregnant women suspicious of PAS. They were referred to this center after the approval of PAS by two expert professors in determining PAS, obtaining informed consent, and registering the criteria of PAS. First, their information and history were collected, such as their obstetrics, abortion, medical, and surgical history. Also, their cesarean section history in its cause, gynecologic and uterine surgery(especially myomectomy), and history of cesarean scar pregnancy(CSP) were recorded. The study excluded women with severe anemia, coagulopathy disorders, emergency status, and severe bleeding before delivery, such as placenta abruption.

One expert perinatal fellowship performed the sonography by Philips affinity 70 system before the surgery based on accreta in FMF. The sonography was accomplished transabdominal by setting the probe vertically without pressure on the pubic symphysis with a full bladder. After locating the placenta (especially placenta previa) and its involvements, the Doppler of right and left uterine arteries, including the pulsatility index(PI), resistance Index(RI), and peak systolic velocity(PSV), were calculated. Also, PSV was documented in the posterior part of the bladder, cervix, the largest lacuna, and the posterior lacuna of the bladder. In the method of uterine Doppler measurement, we placed the probe parallel to the woman's sagittal axis (parasagittal) and perpendicular to the location of the bladder. All pregnant women in this study were delivered electively between 34 to 37 weeks of gestational age based on placental position, especially placenta previa, the severity of accreta, and pregnant women's symptoms, including hematuria. Also, two fixed expert surgeons performed all cesarian sections and probable hysterectomies( because of uncontrolled bleeding and the impossibility of preserving the uterus). In addition, all abdominal incisions were performed by Maylard incisions, and myometrial incisions were vertical in the cases of the placenta previous and Kerr in nonprevias.

Weighting drain sheets and gauzes calculated the average bleeding for each pregnant woman before and after the surgery. Also, because of distinguishing between amniotic fluid(AF) and bleeding, AF was gathered in another suction. In our study, massive bleeding was considered equal to or more than 2500 cc bleeding or requiring more than 3 unit packed red blood cells during the operation (12). Also, other morbidities, such as hysterectomy and admission duration, were documented. In addition, in our study, accreta were classified as type 1 accreta and increta and percreta were classified as type 2 accreta as more invasive based on pathologic reports (13).

The primary outcome was the relationship between the Doppler study and massive bleeding. The secondary outcome was their relationship with needing a hysterectomy, type of accreta, and other surgical morbidities such as bladder and ureteral injury, ICU admission, relaparotomy, and readmission.

### Statistical analysis

All data in this study were analyzed by 22 version of the statistical package for social science (SPSS). A P-value less than 0.05 was

considered significant. Mean, standard deviation, median, maximum, and minimum were obtained for quantitative data. Also, frequency and relative frequency were obtained for qualitative data. The Kolmogorov-Smirnov test checked the normality of data distribution. All quantitative variables in this study had non-normal distribution. Therefore, we used the Mann-Whitney test to investigate the relationship between quantitative variables and massive bleeding, hysterectomy, and pathology outcomes. The Chi-square test investigated the relationship between groups and categories (qualitative variables). Also, the receiver operating characteristic (ROC) curve was performed for variables and showed their specificities and sensitivities as prognostic parameters for PAS.

#### Ethical statement

In implementing all stages of the study, privacy protection and confidentiality of the information obtained from files and other processes were considered. To preserve the pregnant women's information and the administrators not knowing the names of the pregnant women, a code was assigned to each pregnant woman, and in all stages of registration, Data and analyses were used from these codes.

### Results

Fifty-one pregnant women were included in the study (Figure 1), with a mean age of  $35.4\pm4.11$  (median:35.00) years and  $34.4\pm2.14$  weeks of GA (median: 28.00) at sonography at their delivery. Their body mass index (BMI) mean was  $28.33\pm3.53$  kg/m<sup>2</sup> (median: 27.75), and their mean admission was  $4.15\pm1.12$  (median: 4) days. Three had no previous C/S with only a history of myomectomy, 31 had previous elective C/S, and 17 had previous emergent C/S in the non-active phase of labor.

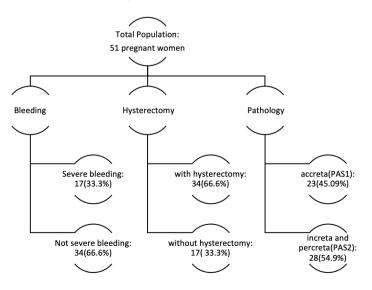


Figure 1. The flow chart of the population study

None of them have emergent C/S in the active phase of labor. In addition, 8 of them have had abortions before. Table 1 In addition, one of them had a ureter injury during the operation

(percreta case with parametrial involvement that was repaired via surgery). Moreover, one pregnant woman had hematuria after the surgery, controlled by cystoscopy and bleeding vessel coagulation in the bladder. There was no laparotomy requirement in the study.

#### Bleeding

Severe Bleeding was seen among 17(33.3%) pregnant women. The median of bladder PSV associated with women with severe bleeding was 57.00(34,90) and 33.00(20,64) among women without severe bleeding (p-value < 0.001).

Also, The median of cervix PSV among women with severe bleeding was 26.00(0.63) and 18.00(0.76) among women without severe bleeding. (p-value=0.037). The median PSV of the left uterine artery noticed among pregnant women with severe bleeding was 89.00(81,135) and 68.00(61,113) for pregnant women without severe bleeding (p-value=0.045).

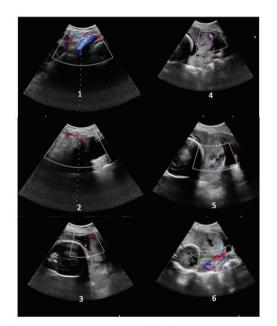
The higher vessels PSV between the bladder and cervix was picked as the highest PSV. The median of the highest PSV for pregnant women with severe bleeding was 57.50(34,90), while 34.00(20,76) for pregnant women without severe bleeding (p-value < 0.001). All measures by Doppler US compared pregnant women with/without severe bleeding are demonstrated in Table 2. Also, Figure 2 shows the appearance of markers on Doppler US.

	1		
Age (years)	35.4±4.11*, 35.00(27,48)**		
Gestational age (weeks)	34.4±2.14*, 28.00(18,38)**		
No previous C/S with only a history of myomectomy	3(5.8%)***		
History of emergent C/S	18(35.29%)***		
History of electiv C/S	31(60.78%)***		
Previous surgery on the uterine	4(7.84%)***		
BMI (Kg/m2)****	28.33±3.53*, 27.75(22,39)**		
Admission days (days)	4.15±1.12*, 4(2, 14)**		
History of abortion 8(15.68%)***			
Type of PAS****			
PAS1	23(45.09%)***		
PAS2	28(54.9%)***		
Hysterectomy after surgery	34(66.66%)***		
Severe blood loos	17(33.33%)***		
*: mean±SD, **: median (min, max), ***: number (%), ****: Body Mass Index, *****: accreta :PAS1, and increta and percreta: PAS2			

Table 1. The characteristic information of thepregnant women

	Severe blood loss (>=2500 ml)	No severe blood loss (<2500 ml)	Total	P-value
Number(%)	17(33.33%)	34(66.66%)	51.00(100%)	
Bladder PSV	57.0(34,90)	33.00(20,64)	41.00(20,90)	< 0.001
Cervix PSV	26.0(0,63)	18.00(0,76)	20.00(0,76)	0.037
The largest lacuna PSV	0.00(0,23)	0.00(0,41)	0.00(0,41)	0.56
The posterior lacuna of the bladder PSV	0.00(0,31)	0.00(0,35)	0.00(0,35)	0.773
The left uterine artery PSV	89.00(81,135)	68.00(61,113)	72.00(61,136)	0.045
The right uterine artery PSV	75.00(60,110)	73.50(51.7,127.0)	74.00(51.7,127.0)	0.298
The mean uterine artery PSV	81(60,110)	71.25(59,107)	73.25(59,110)	0.093
The highest PSV	57.50(34,90)	34.00(20,76)	41.50(20,90)	< 0.001
The left uterine artery PI	0.90(0.60,1.36)	0.77(0.55,1.77)	0.79(0.55,1.77)	0.453
The right uterine artery PI	0.91(0.58,76.00)	0.87(0.54,66.00)	0.89(0.54.76.00)	0.555
The mean PI of the uterine artery	0.91(0.63,38.45)	0.88(0.55,33.30)	0.89(0.55,38.45)	0.075
The left uterine artery RI	0.56(0.39,1.00)	0.49(0.40,0.75)	0.51(0.39,1.00)	0.222
The right uterine artery RI	0.53(0.40,0.66)	0.51(0.40,0.68)	0.51(0.40,0.68)	0.302
The mean RI of the uterine artery	0.53(0.44,0.74)	0.50(0.41,0.68)	0.41(0.41,0.74)	0.110

Pulsatility index(PI), RI(Resistance Index), and peak systolic velocity(PSV)



 The right uterine artery Doppler sonography, 2) The left uterine artery Doppler sonography, 3)The largest lacunae Doppler sonography, 4) The posterior of the bladder Doppler sonography, 5) The posterior lacunae Doppler sonography, 6)Cervix Doppler sonography.

### Figure 2. The Doppler sonography in pregnant women with Placenta Accreta Spectrum

although it was 82.25(70,94) among those who had not had a hysterectomy (p-value=0.001). Moreover, the median of the highest PSV associated with women who had a hysterectomy after their delivery was 46.00(20,90), while it was 39.50(33,46)

among women without hysterectomy (p-value=0.008). All measures by Doppler US compared pregnant women with/ without hysterectomy are demonstrated in Table 3.

### The Pathology of PAS

All pathology was confirmed as PAS. Also, 23 (45.1%) had type 1 PAS, and 28 (54.9%) had type 2 PAS. Women with type 1 PAS had 32.00(20,64)bladder PSV, while 46.00(27,90) among women with type 2 PAS (p-value <0.001).The median cervix PSV associated with the women with type 1 PAS was 18.00(0,38), while it was 25.00(0,76) for women with type 2 PAS (p-value=0.053). Also, the median of PSV of the left uterine artery for pregnant women with type 1 PAS was 68.00(61,113), although it was 77.00(61,135) among women with type 2 PAS (p-value=0.049). In addition, the median of the highest PSV among pregnant women with type 1 PAS was 32.00(20,64), while it was 46.00(27,90) among pregnant women with type 2 PAS (p-value<0.001). All measures by Doppler US compared between pregnant women and the type of pathology are demonstrated in Table 4.

### **Receiver Operating Characteristic (ROC) Curve**

In the ROC curve (Figure 3), the cut-off associated with bladder PSV was 41. Its sensitivity was 84%, and its specificity was 60% (p-value < 0.001). Also, it was noticed that the cut-off associated with cervix PSV was 18.5 with 84% sensitivity and 57% specificity (p-value < 0.001). Moreover, the cut-off for the mean PSV of the artery uterine in the ROC curve was 66.7, with 83% sensitivity

	Hysterectomy No Hysterectomy		P-value
Number(%)	34(66.66%)	17(33.33%)	
Bladder PSV	46.00(20,90)	39.50(33,46)	0.005
Cervix PSV	20,00(0,76)	20.00 (14,26)	0.013
The largest lacuna PSV	0.00(0,18)	12.5(0,25)	0.835
The posterior lacuna of the bladder PSV	0.00(0,27)	0.00(0,0)	0.373
The left uterine artery PSV	68.00(61,135)	82.00(63,101)	0.003
The right uterine artery PSV	70.00(51,125)	82.50(77,88)	0.01
The mean uterine artery PSV	71.50(59,110)	82.25(70,94)	0.001
The highest PSV	46.00(20,90)	39.5(33.46)	0.008
The left uterine artery PI	0.78(0.51,1.75)	1.18(1.15,1.22)	0.406
The right uterine artery PI	0.90(0.54,76.00)	0.72(0.69,0.76)	0.117
The mean PI of the uterine artery	0.89(0.58,38.45)	0.95(0.95,0.96)	0.374
The left uterine artery RI	0.50(0.39,1.00)	0.62(0.62,0.63)	0.147
The right uterine artery RI	0.50(0.40,0.66)	0.48(0.47,0.49)	0.96
The mean RI of the uterine artery	0.51(0.44,0.74)	0.55(0.55,0.55)	0.374

Table 3. The Doppler markers and hysterectomyamong pregnant women

All data are demonstrated in median (minimum, maximum),

Pulsatility index(PI), RI(Resistance Index), and peak systolic velocity(PSV)

and 15% specificity (p-value=0.110). Also, in the ROC curve, we noticed that the cut-off associated with the highest PSV was 38.8, with 84% sensitivity and 60% specificity (p-value=0.033) Table 5.

### Discussion

Evaluating methods and markers (laboratory, US, and characteristic information) are still being investigated to reach appropriate assessment in diagnosis and predicting prognosis of the PAS for the clinicians As Chong et al. declared that a self-made ultrasonic scoring assessment is still a suitable tool to predict the prognosis of the PAS, such as hysterectomy requirement and severe bleeding (14), regardless Marsoosi et al. suggested that the scoring system, including several simple ultrasound and clinical characteristics, could effectively predict the prognosis and severity of the PAS for appropriate clinical judgment(15). This study demonstrated that the Doppler US

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	PAS 1 (accreta)	PAS 2 (increta and percreta)	P-value	
Number(%)	23(45.09%)	28(54.91%)		
Bladder PSV	32.00(20,64)	46.00(27,90)	< 0.001	
Cervix PSV	18.00(0,38)	25.00(0,76)	0.053	
The largest lacuna PSV	0.00(0,41)	0.00(0,25)	0.930	
The posterior lacuna of the bladder PSV	0.00(0,37)	0.00(0,31)	0.373	
The left uterine artery PSV	68.00(61,113)	72.00(61,135)	0.049	
The right uterine artery PSV	70.00(60,125)	77.00(51,127)	0.273	
The mean uterine artery PSV	71.00(62,107)	82.00(59,110)	0.111	
The highest PSV	32.00(20,64)	46.00(27,90)	< 0.001	
The left uterine artery PI	0.77(0.55,1.77)	0.81(0.57,1.74)	0.220	
The right uterine artery PI	0.90(0.54,66)	0.82(0.54,76)	0.289	
The mean PI of the uterine artery	0.88(0.55,33.30)	0.91(0.58,38.45)	0.912	
The left uterine artery RI	0.48(0.40,0.74)	0.51(0.39,1.00)	0.063	
The right uterine artery RI	0.52(0.40,0.65)	0.50(0.40,0.68)	0.971	
The mean RI of the uterine artery	0.50(0.41,0.68)	0.52(0.44,0.74)	0.153	
All data are demonstrated in median (minimum, maximum), Pulsatility				

## Table 4. The Doppler markers and histopathologyamong pregnant women

All data are demonstrated in median (minimum, maximum), Pulsatility index(PI), RI(Resistance Index), and peak systolic velocity(PSV)

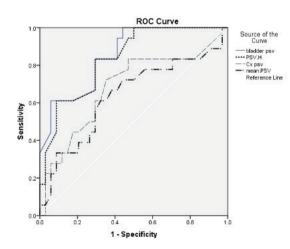


Figure 3. The ROC curve for Bladder PSV, Cervix PSV, the highest PSV, and The mean PSV for diagnosis of Placenta accreta spectrum (PAS)

Parameter	Cut off	AUC*	<b>P.value</b>	Sensitivity	Specifity
Bladder PSV	41	.885	< 0.001	84%	60%
Cervix PSV	18.5	.835	< 0.001	84%	57%
Highest PSV	38.5	.681	0.033	84%	60%
Mean PSV	66.7	.636	0.110	83%	15%
*AUC: area under the curve					

### Table5. The Diagnostic ability of DopplerUltrasonography by ROC curve

markers could be appropriate assessments to clarify the severity of the PAS facing pregnant women and clinicians, like severe bleeding, hysterectomy requirement, and histopathology with significant sensitivity and specificity.

Previously, some studies suggested novel markers in Doppler US to evaluate the prognosis of PAS and to choose a better assessment. Al-Khan et al. indicated that the presence of posterior urinary bladder wall pulsatile arterial vessels with low RI could be a suitable marker to predict the severity of the PAS (15). Our study investigated Bladder PSV and showed that it is associated significantly with severe bleeding, hysterectomy requirements, and invasive histopathology among pregnant women with PAS. It can be used as a diagnostic tool with appropriate sensitivity (84%) and specificity(60%).

Yule et al. showed that women confirmed with PAS who needed hysterectomy after the delivery noticed an increase in color pixel area near the bladder-uterine serosal interface in the transvaginal color Doppler US in the first trimester (16). The current study did not evaluate women in the first trimester and was limited to women in the third trimester and used the trans-abdominal method. Also, our study found no significant relationship between the PSV of the posterior lacuna of the bladder and PAS outcomes.

Some studies investigated the association between placenta accreta invasion and the Doppler US. For example, Hossein et al. reported that markers like "Numerous coherent vessels involving the serosa–bladder interface" in 2D and 3D Doppler sonography could be an independent marker to predict the severity and the complications facing pregnant women with PAS (12); also, Firmansha et al. showed that the flow index value in 3D doppler sonography could predict the depth of the invasion of the PAS among pregnant women before the surgery and the blood loss level (18). The current study showed that the bladder PSV, the highest PSV, and the left uterine artery PSV are significantly associated with invasive forms of PAS (increta and percreta).

In addition to the above findings, our study supported that cervix PSV is associated with severe bleeding and a higher rate of hysterectomy among women with PAS; also, it could be an appropriate marker with reasonable sensitivity and specificity to diagnose the PAS among women with probable PAS to decide better decision for their pregnancy and delivery; moreover, left uterine artery PSV was a novel marker compared to previous studies and publication in diagnosis and predicting prognosis of PAS.

In our study, we used one expert prenatal fellowship and two constant surgeons for cesarean section and hysterectomy if needed; therefore, the difference in the process was minimized. Also, the emergent deliveries were excluded, so the blood loss due to the emergent situation was diminished. Moreover, findings at the surgery and the following histopathology confirmed that all pregnant women enrolled in the study were diagnosed with PAS with the appropriate criteria.

This study has some limitations; for example, A small population due to the rate of the PAS was one of our limitations. Also, the single-center study was the other limitation of this study. The higher rate of hysterectomy among the pregnant women was a limitation that showed the higher invasive and severe form of PAS among the pregnant women in our study because many pregnant women with probable complicated PAS were referred to this center as a referral center; however, many markers were meaningful in our research despite this limitation.

Further studies with a large-scale population are required to clarify better the association between these markers and PAS outcomes, especially markers that differed between groups but not statistically. Moreover, using transvaginal US in addition to transabdominal US and evaluating these markers in all trimesters among pregnant women separately could be appropriate in future research.

### Conclusion

Bladder PSV, cervix PSV, and mean PSV between uterine arteries were confirmed as novel markers to predict the complications facing women with PAS, such as severe bleeding and hysterectomy. Also, these markers could predict the invasive forms of PAS(increta and percreta). Clinicians and surgeons can use these markers in Doppler US as a non-invasive tool in the third trimester to choose the appropriate management for pregnant women and decrease the morbidities and mortalities among them.

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